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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/616,649	07/09/2003	Judy H. Chiao	24852-501 CIP2	9975

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EXAMINER	
GRAFFEO, MICHEL	
ART UNIT	**PAPER NUMBER**
1614	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/616,649	CHIAO ET AL.	
	Examiner	Art Unit	
	Michel Graffeo	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-270* is/are pending in the application.

4a) Of the above claim(s) *2-5,20-33 and 48-270* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-19 and 34-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 7/25/06 · 6/9/05 · 1/15/05 · 3/14/05 · 9/13/05 · 4/6/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I in the reply filed on 6 October 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 2-5, 20-33 and 48-270 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim.

Status of Action

Claims 1, 6-19 and 34-47 are examined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 6, 11 and 34-35 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent No. 6905669 to DeMartino.

DeMartino teaches the treatment of lymphomas comprising SAHA (see col 5 lines 40-45 and col 6 line 20) wherein the dosage is administered orally (see col 6 line 64) and at a dosage of from 2-100 mg/m^2 (see col 7 lines 15-20).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 1, 6-19 and 34-47 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Richon *et al.* (US 2003/0235588 A1) in view of Rubartelli *et al.* (Cancer Research, 1995, vol. 55, pages 675-680).

The instant claims are drawn to a method of treating diffuse T-cell lymphoma comprising oral administration of SAHA.

Richon *et al.* disclose methods of treating thioredoxin (TRX)-mediated diseases by administering to a subject in need of such treatment a therapeutically effective amount of a histone deacetylase (HDAC) inhibitor or a pharmaceutically acceptable salt or hydrate thereof (Abstract). Elevated levels of TRX have been found in cancer. As such, TRX can "stimulate proliferation of a wide variety of cancer cell lines and inhibit apoptosis in cells over expressing the protein" (page 1, ¶ [0007]). The invention discloses the use of HDAC inhibitors that can alter the expression of a TRX-binding protein (*e.g.* TRX-binding protein-2 or TBP-2), which in turn can lead to altered TRX/TBP-2 cellular binding interaction, resulting in an increase or decrease in the level or activity of cellular TRX (pages 1-2, ¶ [0011]). Thus, the invention relates to the use of HDAC inhibitors in a wide variety of TRX-mediated diseases and conditions, including diseases characterized by cellular hyperproliferation (*id.*).

The inventors discovered that HDAC inhibitors induce expression of a TRX-binding protein, which is associated with a decrease in the level or activity of TRX resulting from interaction of TRX with the TRX-binding protein (page 2, ¶ [0012]). HDAC inhibitors, therefore, can be used to treat diseases characterized by "an increased level or activity of TRX" (page 2, ¶ [0013]). HDAC inhibitors effective at treating TRX-mediated diseases include hydroxamic acid derivatives (page 2, ¶ [0021]), including the instantly claimed SAHA (*id.* at ¶ [0023] and page 3, ¶ [0030]).

Pharmaceutically acceptable salts of HDAC inhibitors are recited at page 17, ¶ [0156]. Hydrates of HDAC inhibitors are recited at page 17, ¶ [0157].

HDAC inhibitors of the invention can be administered in oral forms including tablets, capsules, pills, powders, granules, elixers, tinctures, suspensions, syrups, and emulsions (page 18, ¶ [0176]). Oral dosages of the HDAC inhibitors can range between about 2 mg to about 2000 mg per day and specific oral dosages of 2, 20, 200, 400, 800, 1200, 1600, and 2000 mg per day are disclosed (page 19, ¶ [0181]). The reference thus discloses the oral dosages of SAHA instantly claimed. The total daily amount of HDAC inhibitor can be administered in multiple doses, such as twice, three, or four times per day (*id.*) and varied per week (see ¶ [0183]). The oral formulations can be in the form of tablets or capsules and combined with pharmaceutically acceptable inert carriers, including microcrystalline cellulose and gelatin binders (page 20, ¶ [0191]). In addition, suitable binders, lubricants and disintegrating agents can be included in the formulation (*id.*). Suitable disintegrating agents include the instantly claimed sodium croscarmellose (*id.*). Suitable lubricants include the instantly claimed magnesium stearate (*id.*).

Thus, Richon *et al.* disclose methods of administering the instantly claimed HDAC inhibitor in the doses and formulations instantly claimed. The reference further discloses methods of treating TRX-mediated diseases. The reference does not explicitly disclose the treatment of diffuse B-cell lymphoma by orally administering SAHA.

However, Rubaertelli *et al.* provide the nexus between TRX and lymphoma and further provide the motivation to use the methods disclosed in Richon *et al.* to treat lymphoma. The reference discloses that exogenous TRX exerts cytokine activities, such as induction of cell proliferation in neoplastic T and B lymphocytes (page 675, left column, second full paragraph). Secretion of TRX is developmentally regulated in normal B and T lymphocytes and is more abundant in activated than in resting lymphocytes (*id.*). Thus, TRX has growth-promoting activity in neoplastic T-lymphocytes.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

In the instant case, the prior art discloses methods of treating TRX-mediated diseases comprising oral administration of HDAC inhibitors in the doses instantly claimed (Richon *et al.*). The prior art also provides the nexus between TRX and growth-promotion of neoplastic B-lymphocytes (Rubartelli *et al.*).

The prior art does not explicitly disclose the treatment of T-cell lymphoma comprising the oral administration of SAHA. However, given the scope and contents of the prior art the instantly claimed methods would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

The level of ordinary skill in the art is that of an M.D., Ph.D. or pharmacist. The skilled artisan would have been aware that T-cell lymphoma could be characterized as a TRX-mediated disease given the disclosure of Rubartelli *et al.*

It was well known in the art that SAHA is capable of inducing tumor cell growth arrest, differentiation and/or apoptosis (Specification, page 4, lines 29-31). As such, one skilled in the art would have appreciated that the methods described in Richon *et al.* would be useful in the treatment of cancers wherein TRX is implicated. In fact, Richon *et al.* contemplate such a treatment of diseases characterized by cellular hyperproliferation (*e.g.* cancer).

Given the above analysis, the instantly claimed methods of treating T-cell lymphoma would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Richon *et al.* disclose the instantly claimed HDAC inhibitor as well as oral formulations and doses commensurate in scope with the instant claims. Rubartelli *et al.* provide the nexus and motivation to use the methods disclosed in Richon *et al.* to treat lymphomas. As such, the skilled artisan would have had the means and motivation to treat B-cell lymphoma with an oral formulation of the HDAC inhibitor, SAHA.

Claims 16-19 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Richon *et al.* and Rubartelli *et al.* as applied to claims 1, 6-19 and 34-47 above, and further in view of Kelly *et al.* (Proc. American Society of Clinical Oncology, 2001, 20:87a, Abstract No. 344) (cited by applicants in IDS filed 6/9/2005 C69).

This instant claims recite administration of oral SAHA three to five day per week and for 14 consecutive days in a 21 day schedule.

Richon *et al.* and Rubartelli *et al.* disclose as discussed *supra*. The combined references do not disclose the specific administration schedules instantly claimed.

However, Kelly *et al.* is provided as evidence that optimizing administration schedules of SAHA is well within the level of ordinary skill in the art and is therefore routine optimization. The reference discloses the optimization of dosing regimes for intravenous SAHA. SAHA was administered to patients at varying doses as a 2-hr. IV infusion for three consecutive days every 21 days and for five consecutive days for 1-3 weeks.

The skilled artisan would have been highly motivated to determine the optimal dose and schedule of administration of SAHA for the treatment of T-cell lymphoma. It is noted that optimization of drug dosing and scheduling is routine in the art of cancer therapy. For example, Phase I and Phase II clinical trials both focus on determining such parameters, as well as determining the efficacy and toxicity of the administered drug. Thus, the instantly claimed dosing regimes of oral SAHA would have been *prima facie* obvious as they would have been readily determined by the skilled artisan from routine optimization of the methods and dosing schedules disclosed in Richon *et al.*

Claims 1, 11-19, 34-35 and 40-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6905669 to DeMartino.

DeMartino teaches the treatment of lymphomas comprising SAHA (see col 5 lines 40-45 and col 6 line 20) wherein the dosage is administered orally (see col 6 line 64) and at a dosage of from 2-100 mg/m^2 (see col 7 lines 15-20). Although the reference does not teach the specific daily dosages, one of ordinary skill in the art would appreciate the variations of safe and efficacious dosages to depend on a patients' sensitivities and needs and find the claimed dosages through routine optimization of dosage amounts.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michel Graffeo whose telephone number is 571-272-8505. The examiner can normally be reached on 9am to 5:30pm Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

30 December 2006
MG

Ardin H. Marschel 1/5/07
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SUPERVISORY PATENT EXAMINER